National Institutes of Health
National Institute of Allergy
and Infectious Diseases

Understanding Vaccines

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institute of Allergy
and Infectious Diseases

NIH Publication No. 98–4219
January 1998

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Preface

This booklet contains information about vaccines to help you understand how they are made and tested, as well as why they can prevent disease. You will not find everything there is to know about vaccines here, however. In fact, the booklet may prompt you to think of more questions about vaccines. After all, vaccines themselves—the developing, manufacturing and testing of them—are complex, as are the diseases they are meant to prevent.

We have tried to anticipate which terms in the booklet will need further definition and clarification. Those terms, when they first appear in the text, are in *italics.* Italicized words and phrases and basic vaccine terminology are defined in the **Glossary** at the end of the booklet.

You may be able to find more in-depth and detailed resources at your local library or through your health care provider. The Internet can be a valuable source as well. Start with the National Institutes of Health (NIH) Web site at **http://www.nih.gov** for information on the broad range of research conducted by NIH. For information on vaccine research, go to **http://www.niaid.nih.gov**, the Web site for the National Institute of Allergy and Infectious Diseases.

Introduction

More than two hundred years ago, Edward Jenner, a country physician practicing in England, noted that milkmaids rarely suffered from smallpox, a disease that was known to kill up to 40 percent of those who contracted it. The milkmaids often did get cowpox, a related but far less serious disease, and those who did, never became ill with smallpox. In an experiment that was to prove a revelation, Jenner took a few drops of fluid from a skin sore of a woman who had cowpox and injected the fluid into the arm of a healthy young boy who had never had cowpox or smallpox. Six weeks later, Jenner injected the boy with fluid from a smallpox sore, but the boy remained

Edward Jenner vaccinates a child for smallpox

free of the dreaded smallpox. Dr. Jenner had discovered one of the fundamental principles of immunization. He had used a relatively harmless foreign substance to evoke an immune response that would protect someone from a disease-causing *microbe.*

In those days, a million people died from smallpox each year in Europe alone, most of them children. Those who survived were often left with grim reminders of their ordeals: blindness, deep scars, deformities. When Jenner laid the foundation for modern vaccines in 1796, he started on a course that would ease the suffering of people around the world. By the beginning of this century, vaccines for rabies, diphtheria, typhoid fever and plague were in use, in addition to the vaccine for smallpox.

Yet vaccination was not immediately accepted. The idea of deliberately introducing a potentially harmful microbe into people was met with suspicion and even outrage by many in the medical and scientific communities, and public opinion was bitterly divided over the merits of vaccination. It took some time to convince people that the benefits of vaccination outweigh the few risks. Today's vaccines are far safer and more protective than those early vaccines. And as science advances, we are developing even better vaccines to protect ourselves from disease.

Benefits

Disease prevention is the key to public health. Vaccines benefit in particular the people who receive them, and in turn, those people cannot spread disease to others who have not been vaccinated. Infection cannot spread if it never gains a foothold. Infectious diseases cause enormous suffering, strain the capabilities of our health care system, and deplete financial resources. For the individual, the health care provider, and in the interest of conserving human and financial resources, it is always better to prevent a disease than to treat it.

Veterinary vaccines benefit people, too. Some diseases, such as rabies, anthrax, certain types of encephalitis, and Rift Valley fever, are readily transmissible from animal species to humans. In many instances, livestock and pets are vaccinated not only for their own health, but for that of their owners.

Common Vaccine-Preventable Diseases

- Chickenpox
- Hepatitis A
- Hepatitis B
- Hib disease
- Influenza
- Measles
- Mumps
- Pertussis (whooping cough)
- Pneumococcal pneumonia
- Polio
- Rubella (German measles)

In the United States, federal and state public health programs help assure that children receive vaccines. Many childhood diseases that were a normal part of growing up just 50 years ago are now preventable. Measles, rubella (German measles), mumps, pertussis, (whooping cough), and chickenpox were almost unavoidable. Most people did not reach adulthood without their families or circle of friends being touched by a serious illness or death caused by an infectious disease. For the most part, children suffered through the course of the disease and were left with *naturally acquired immunity*, some school work to catch up on, and perhaps a little pockmark somewhere on their skin. However, in some cases, children died, or they were left with permanent loss of hearing or sight or other tragic effects of serious infections.

Adult Immunization

Although most of us receive the great majority of our immunizations during childhood, it is important to remember that vaccines are not just for young children. Adolescents and adults should keep up-to-

date on tetanus and diphtheria immunizations. Adults who have not had diseases such as measles or chickenpox during childhood, or the vaccines to prevent them, should consider being immunized. Ironically, childhood diseases such as measles, mumps, and chickenpox can be far more serious in adults.

People who travel overseas should determine, together with their physicians or at international travel clinics, which vaccines would be appropriate based on their destinations. Effective vaccines are available to prevent yellow fever, polio, typhoid fever, hepatitis A, cholera, and other bacterial and viral diseases that are more prevalent abroad than in the United States.

Each year, as we prepare for winter and the flu season, many adults should consider the benefits of the flu vaccine. In addition to flu vaccine, immunizations for pneumococcal pneumonia, hepatitis A, and hepatitis B are recommended for people who may be at risk.

Evaluating a Vaccine

Variations in individuals and their immune systems are many and subtle; thus no vaccine is totally effective. In the United States, a vaccine is approved for general use if it fulfills several stringent requirements.

- The vaccine must be safe. Although it is quite unlikely that a vaccine will ever be 100 percent safe, it must produce *protective immunity* with only minimal side effects (such as redness and soreness at the vaccination site) for the overwhelming majority of those who receive it. More discomfort in side effects can be acceptable, however, depending upon the severity of the disease the vaccine is designed to prevent. For example, most people would consider vaccine side effects that mimicked the symptoms of a bad cold acceptable if the vaccine protected them from HIV disease.

Vaccines Licensed in the United States

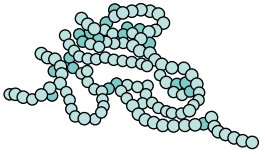
- Adenovirus vaccine
- Anthrax vaccine
- Bacille Calmette-Guérin vaccine
- Cholera vaccine
- Diphtheria toxoid
- Diphtheria and tetanus toxoids
- Diphtheria and tetanus toxoids and acellular pertussis vaccine
- Diphtheria and tetanus toxoids and whole cell pertussis vaccine
- Diphtheria and tetanus toxoids and pertussis and *Haemophilus influenzae* b (Hib) conjugate vaccine
- Hib conjugate vaccine (with diphtheria, meningococcal, and tetanus conjugates)
- Hepatitis A vaccine
- Hepatitis B vaccine
- Influenza virus vaccine
- Japanese encephalitis virus vaccine
- Measles virus vaccine
- Measles and mumps virus vaccine
- Measles, mumps, and rubella virus vaccine
- Meningococcal vaccine, Group A
- Meningococcal vaccine, Group C
- Meningococcal vaccine, Groups A and C
- Meningococcal vaccine, Groups A, C, Y, and W-135
- Mumps virus vaccine
- Pertussis vaccine (acellular)
- Pertussis vaccine (whole cell)
- Plague vaccine
- Pneumococcal vaccine
- Poliovirus vaccine—inactivated
- Poliovirus vaccine—live, attenuated
- Rabies vaccine
- Rubella vaccine
- Smallpox vaccine
- Tetanus toxoid
- Typhoid vaccine
- Varicella (chickenpox) virus vaccine
- Yellow fever vaccine

- The vaccine must be *immunogenic*, that is, it must cause a strong and measurable immune response. Vaccines usually contain *antigens*, bits of material, sometimes from the disease-causing microbe itself, that can stimulate the immune system to respond and fight off a potential infection. When a vaccine is immunogenic, it primes the recipient's immune system to recognize the disease-causing microbe and launch a counterattack before illness can occur. In addition, the vaccine must induce the right type of immunity. When microbes invade, they cause disease in different ways, and different parts of the immune system respond to fight them. Vaccines must stimulate the specific parts of the immune system that protect against a particular kind of organism.
- The vaccine must be stable during its shelf life, that is to say, its *potency* must remain at the proper level for the vaccine to evoke an immune response. Many *inactivated vaccines* are simple to store, since they are in powdered form and are reconstituted with the appropriate fluid before they are given. *Live, attenuated vaccines*, however, require refrigeration from manufacturer to clinic to maintain stability and potency.

All approaches to vaccine development focus on the immune system and the body's natural defenses against foreign invaders. To understand something of how vaccines work, it is best to start with the immune system. Together, your immune system and vaccines are powerful allies in the fight against disease.

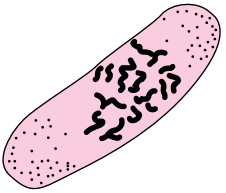
Protection Against Microbes

The body has an arsenal of defenses that it uses to ward off foreign invaders. Healthy immune systems recognize as foreign many things that are not self.

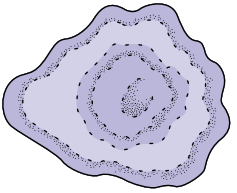


Bacteria: streptococci

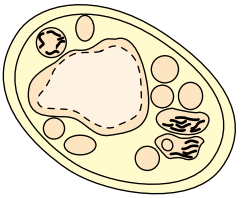
Most of the foreign invaders that confront the human immune system are microscopic. Fungi, parasites, bacteria, and viruses populate our planet in far greater numbers than any other living organisms. Some are beneficial. We coexist quite happily with certain types



Parasite: malaria



Virus: herpes simplex virus



Fungus: candida

of bacteria that live in our gastrointestinal and genital tracts. These bacteria help prevent infection by harmful organisms. We are even dependent on some microorganisms that inhabit our gastrointestinal tracts for their help in digesting food. Whether beneficial or harmful, however, all foreign microbes in the human body display special markers on antigens called antigenic determinants or *epitopes.* It is these antigens and their determinants that the immune system may recognize as harmful and identify for destruction.

The Immune System

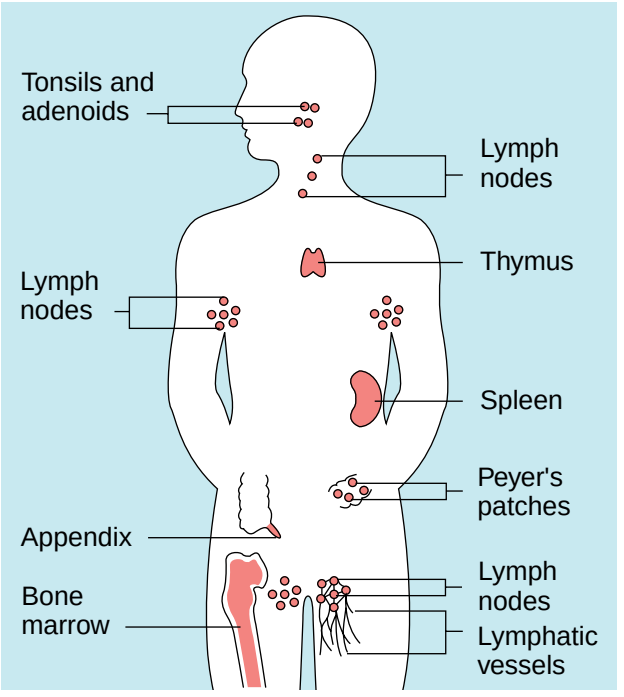
Organs of the Immune System

The immune system is a complex of organs—highly specialized cells and even a circulatory system separate from blood vessels—all of which work together to clear infection from the body.

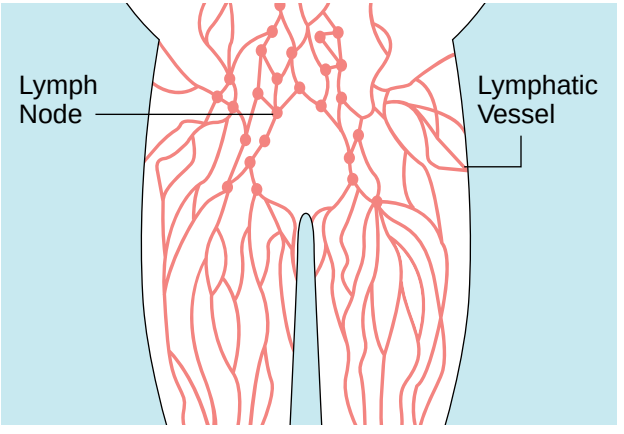
The organs of the immune system, positioned throughout the body, are called *lymphoid* organs. The word *"lymph"* in Greek means a pure, clear stream—an appropriate description considering its appearance and the purpose of our immune systems.

Lymphatic vessels and *lymph nodes* are the parts of the special circulatory system that carries lymph, a transparent fluid containing white blood cells, chiefly *lymphocytes.* Lymph bathes the tissues of the body, and the lymphatic vessels collect and move it eventually back into the blood circulation. Lymph nodes dot the network of lymphatic vessels and provide meeting grounds for the immune system cells that defend against invaders. The *spleen,* at the upper left of the abdomen, is also a staging ground and a place where immune system cells confront foreign microbes.

Organs and tissues of the immune system dot the body in a protective network of barriers to infection.



Lymphatic vessels form a circulatory system that operates in close partnership with blood circulation.



Pockets of lymphoid tissue are in many other locations throughout the body, such as the *bone marrow* and *thymus*. Tonsils, adenoids, *Peyer's patches*, and the appendix are also lymphoid tissues.

Both immune cells and foreign molecules enter the lymph nodes via blood vessels or lymphatic vessels. All immune cells exit the lymphatic system and eventually return to the bloodstream. Once in the bloodstream, lymphocytes are transported to tissues throughout the body, where they act as sentries on the lookout for foreign antigens.

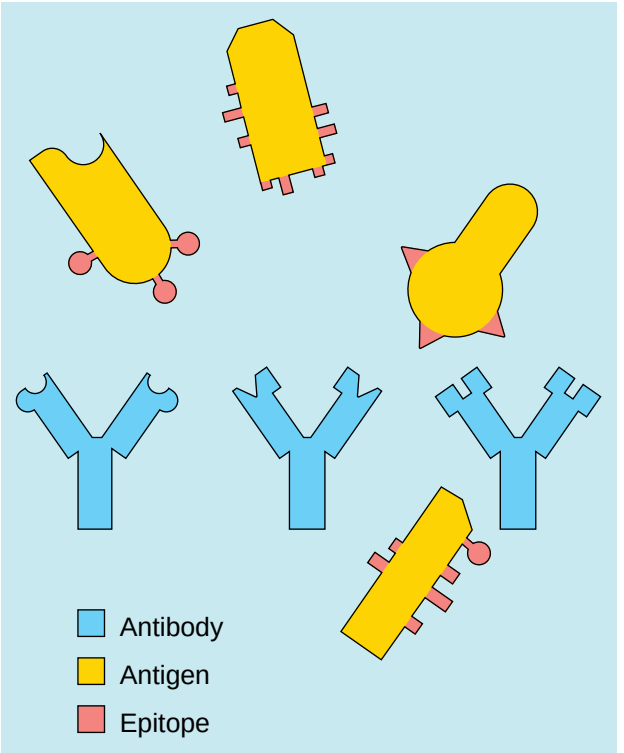
How the Immune System Works

Cells that will grow into the many types of more specialized cells that circulate throughout the immune system are produced in the bone marrow. This nutrient-rich, spongy tissue is found in the center shafts of certain long, flat bones of the body, such as the bones of the pelvis. The cells most relevant for understanding vaccines are the lymphocytes, numbering close to one trillion.

The two major classes of lymphocytes are *B cells*, which grow to maturity in the bone marrow, and *T cells*, which mature in the thymus, high in the chest behind the breastbone.

B cells produce *antibodies* that circulate in the blood and lymph streams and attach to foreign antigens to mark them for destruction by other immune cells. B cells are part of what is known as *antibody-mediated* or *humoral immunity*, so called because the antibodies circulate in blood and lymph, which the ancient Greeks called, the body's "humors." Certain T cells, which also patrol the blood and lymph for foreign invaders, can do more than mark the antigens; they attack and destroy diseased cells they recognize as foreign. T cell lymphocytes are responsible for *cell-mediated immunity* (or *cellular immunity*). T cells also orchestrate, regulate and coordinate the overall immune response. T cells depend on unique cell surface molecules called the *major histocompatibility complex* (MHC) to help them recognize antigen fragments.

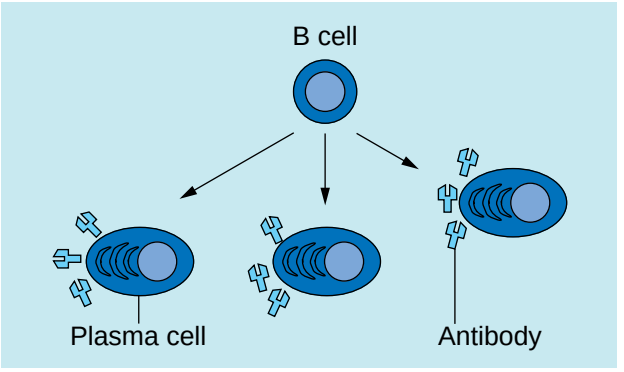
Antibodies produced by cells of the immune system recognize foreign antigens and mark them for destruction.



Antibodies

The antibodies that B cells produce are basic templates with a special region that is highly specific to target a given antigen. Much like a car coming off a production line, the antibody's frame remains constant, but through chemical and cellular messages, the immune system selects a green sedan, a red convertible or a white truck to combat this particular invader. However, in contrast to cars, the variety of antibodies is very large. Different antibodies are destined for different purposes. Some coat the foreign invaders to make them attractive to the circulating scavenger cells, *phagocytes*, that will engulf an unwelcome microbe. When some antibodies combine with antigens, they activate a cascade of nine proteins, known as *complement*, that have been circulating in inactive form in the blood. Complement forms a partnership with antibodies, once they have reacted

B lymphocyte cells become plasma cells, which produce antibodies when a foreign antigen triggers the immune response.

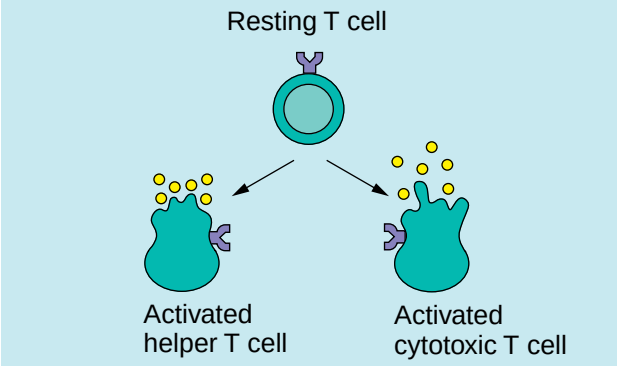


with antigen, to help destroy foreign invaders and remove them from the body. Still other types of antibodies block viruses from entering cells.

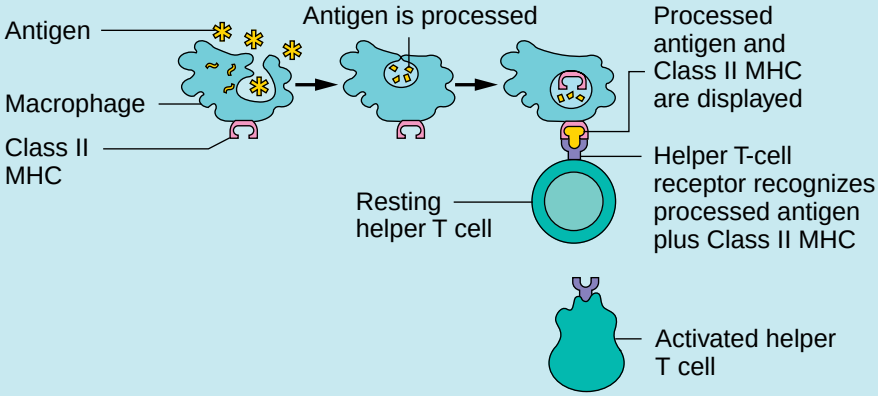
T Cells

T cells have two major roles in immune defense. Regulatory T cells are essential for orchestrating the response of an elaborate system of different types of immune cells. *Helper T cells*, for example, also known as CD4 positive T cells (CD4+ T cells), alert B cells to start making antibodies; they also can activate other T cells and immune system scavenger cells called *macrophages* and influence which type of antibody is produced. Certain T cells, called CD8 positive T cells (CD8+ T cells), can become killer cells that attack and destroy infected cells. The *killer T cells* are also called *cytotoxic T cells* or CTLs (cytotoxic lymphocytes).

T lymphocytes become CD4+ or helper T cells, or they can become CD8+ cells, which in turn can become killer T cells, also called cytotoxic T cells.

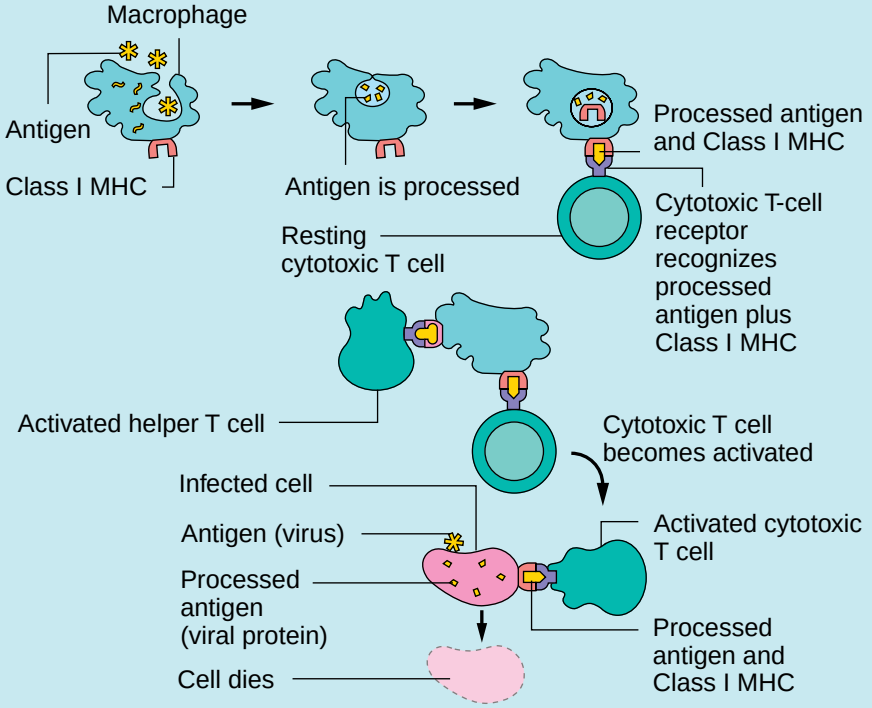


Activation of helper T cells



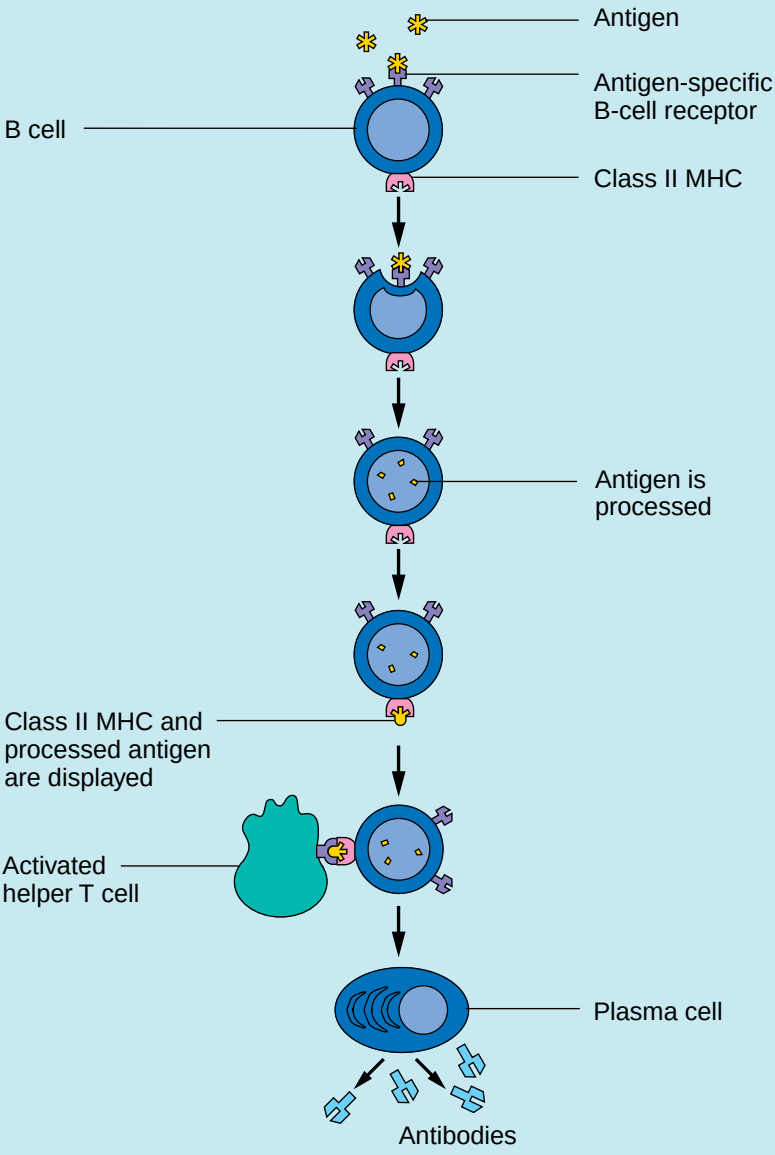
After it engulfs and processes an antigen, the macrophage displays the antigen fragments combined with a Class II MHC protein on the macrophage cell surface. The antigen-protein combination attracts a helper T cell, and promotes its activation.

Activation of cytotoxic T cells



After a macrophage engulfs and processes an antigen, the macrophage displays the antigen fragments combined with a Class I MHC protein on the macrophage cell surface. A receptor on a circulating, resting cytotoxic T cell recognizes the antigen-protein complex and binds to it. The binding process and a helper T cell activate the cytotoxic T cell so that it can attack and destroy the diseased cell.

Activation of B cells to make antibody



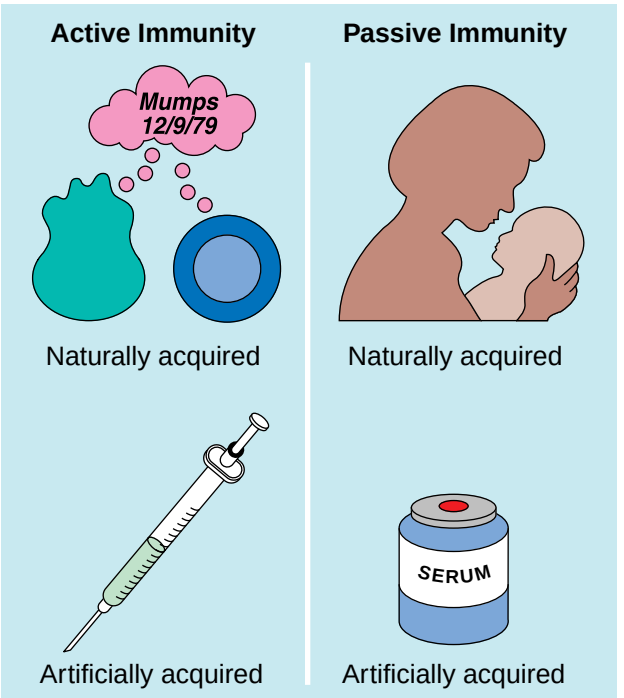
A B cell uses one of its receptors to bind to its matching antigen, which the B cell engulfs and processes. The B cell then displays a piece of the antigen, bound to a Class II MHC protein, on the cell surface. This whole complex then binds to an activated helper T cell. This binding process stimulates the transformation of the B cell into an antibody-secreting plasma cell.

Naturally Acquired Immunity

As early as 2500 years ago in Greece, some people understood enough about contagion to know that a person who had recovered from plague would not get it again. Later, physicians recognized that a person acquires immunity to many diseases in this way.

This protection comes from another special cell of the immune system. Whenever B cells and T cells are summoned, they transform some of their numbers into *memory cells.* Although the army of antibodies necessary to destroy an infectious agent does not remain, the memory cells do. If the memory cells recognize the invader again, the immune system quickly mounts a defense and defeats the interlopers before illness can occur. This type of immunity is naturally acquired. Most of us benefit from naturally acquired immunity from our earliest days. Certain types of immune cells are passed from mother to fetus during pregnancy. Thus, most newborns, though vulnerable in many ways, have a head start in fighting disease.

We become immune through artificial and natural means. Vaccines give us artificially acquired active immunity to disease.



Artificially Acquired Immunity

Artificially acquired immunity can be either passive or active. Artificially acquired passive immunity results when antibodies produced by another animal or human are given to someone to prevent or treat disease. For example, administering tetanus antitoxin or rabies immune globulin to someone is a way of conferring passive immunity. This type of immunization is effective very quickly, but since it lasts only a short time, it is used to protect people when they are particularly vulnerable, such as immediately after exposure to a serious disease. Artificially acquired active immunity, the type obtained from vaccines, is essentially the subject of this booklet.

Artificially acquired active immunity is achieved through safe and effective vaccines. Traditional vaccines are preparations of killed or weakened bacteria or viruses, or parts of these microbes, or *inactivated toxins* from the disease-causing agent. Recently, innovative vaccine technologies have revealed many more ways to give people active immunity to a disease. These include *subunit vaccines, conjugate vaccines* and *naked DNA vaccines.*

Different Types of Vaccines

When a new disease emerges or a familiar one becomes a more significant health threat than it has been in the past, scientists, physicians and public health workers recognize the need for a new way to prevent the disease. Once scientists have identified the organism or toxin that causes the illness, they pursue a number of approaches to develop a vaccine.

Vaccine development has its early roots in the work of Edward Jenner, who discovered how to protect people from smallpox, and Louis Pasteur, who developed a vaccine to protect from rabies. Those pioneering efforts subsequently led to vaccines for diseases that had once claimed millions of lives worldwide.

The purpose of a vaccine is to bring about active immunity by provoking a response from a person's immune system—marshaling B and T cells to swing into action—and creating a memory within the immune system so that exposure to the active disease agent will stimulate an already primed immune system to fight the disease. Some vaccines are combinations that protect against several diseases. Most of us are familiar with the DTP (diphtheria, tetanus, pertussis) and MMR (measles, mumps, rubella) vaccines that children in the United States receive. Scientists extensively test these combination vaccines to make sure that none of the antigens detracts from the immune priming effect of the others. Thus the vaccines can provide triple protection, the recipients are spared extra needle sticks, and the public health costs are reduced.

Based on the biological and chemical characteristics of the disease-causing agent and on what type of immunity is desired, researchers begin to develop one of the following types of vaccines. Vaccines can be produced from 1) inactivated (killed), 2) live, attenuated (weakened), or 3) synthetic (laboratory-made) microbial materials.

Traditional Vaccines

Inactivated Vaccines

Inactivated vaccines are produced by killing the disease-causing microorganism with chemicals or heat. Such vaccines are stable and safe; they cannot revert to the *virulent* (disease-causing) form. They often do not require refrigeration, a quality that makes them accessible to the people of many developing countries, as well as practical for vaccinating people who are highly mobile, such as members of the armed forces. However, most inactivated vaccines stimulate a relatively weak immune response and must be given more than once. A vaccine that requires several doses (boosters) has a limited usefulness, especially in areas where people have less access to regular health care.

The flu shot is an inactivated vaccine, as are the vaccines for cholera, plague, and hepatitis A.

Live, Attenuated Vaccines

To make a live, attenuated vaccine, the disease-causing organism is grown under special laboratory conditions that cause it to lose its virulence, or disease-causing properties. Although live vaccines require special handling and storage in order to maintain their potency, they produce both antibody-mediated and cell-mediated immunity and generally require only one boost, or additional dose. Most live vaccines are injected; some, however, such as the polio vaccine, are given orally. In addition, intranasal vaccines, administered in the nose, show promise in preventing flu.

While there are advantages to live vaccines, there is one caution. It is the nature of living things to change, to *mutate*, and the organisms used in live vaccines are no different. There is a remote possibility that the organism may revert to a virulent form and cause disease. It is for this reason that live vaccines continue to be carefully tested and monitored.

For their own protection, people with compromised immune systems—such as people who are taking *immunosuppressive* drugs, people who have cancer or people living with HIV—are usually not given live vaccines.

The vaccines for yellow fever, measles, rubella, and mumps are all produced from live, attenuated organisms.

Toxoids

A *toxoid* is an inactivated toxin, the harmful substance produced by a microbe. Many of the microbes that infect people are not themselves harmful. It is the powerful toxins they produce that can cause illness. For example, the bacterium that causes tetanus is found everywhere in nature, and in an environment with plenty of oxygen, it is harmless. If that same organism is put into an environment without oxygen,

however, the organism starts to change and produce tetanus toxin, a substance far more potent than the well-known poison sodium cyanide. To inactivate such powerful toxins, vaccine manufacturers treat them with materials known to completely cripple any disease-causing ability. *Formalin*, a solution of formaldehyde and sterile water, is most often used to inactivate toxins and produce toxoids.

Toxoids are used to immunize people against tetanus and diphtheria.

New and Second-Generation Vaccines

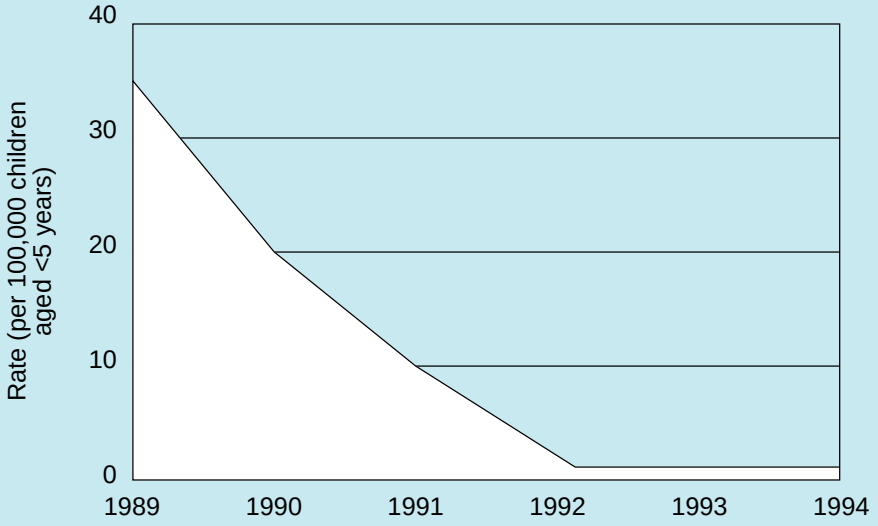
Scientists are using new technologies to improve traditional vaccines. These new second-generation vaccines, as well as vaccines for diseases that had not been preventable very long ago, are made using powerful techniques such as *recombinant genetic engineering* (also called *recombinant DNA technology*).

Conjugate Vaccines

The bacteria that cause some diseases, such as pneumococcal pneumonia and certain types of meningitis, have special outer coats. These coats disguise antigens so that the immature immune systems of infants and younger children are unable to recognize these harmful bacteria. In a conjugate vaccine, proteins or toxins from a second type of organism, one that an immature immune system can recognize, are linked to the outer coats of the disease-causing bacteria. This enables a young immune system to respond and defend against the disease agent.

Currently, conjugate vaccines are available to protect against a type of bacterial meningitis caused by *Haemophilus influenzae* type b (Hib). Meningitis, an inflammation of the fluid-filled membranes that protect the brain and spinal cord, can be fatal, or it can cause severe, life-long disabilities such as deafness and mental retardation. Since Hib vaccines

Incidence rate of invasive *Haemophilus influenzae* type b (Hib) disease among children aged <5 years, United States, 1989-1994



Hib-caused diseases among children have plummeted since 1989, when Hib vaccines became widely used.

Source: Summary of Notifiable Diseases, United States, 1995. CDC Morbidity and Mortality Weekly Report

have been in widespread use in the United States, Hib meningitis has nearly disappeared among babies and young children.

Subunit Vaccines

Sometimes vaccines developed from antigenic fragments are able to evoke an immune response, often with fewer side effects than might be caused by a vaccine made from the whole organism. Subunit vaccines can be made by taking apart the actual microbe, or they can be made in the laboratory using genetic engineering techniques.

Today, subunit vaccines are used to protect against pneumonia caused by *Streptococcus pneumoniae* and against a type of meningitis.

A *recombinant subunit vaccine* for hepatitis B virus infection is now licensed for use in the United States. The recombinant vaccine is made by inserting a tiny portion of the hepatitis B virus' genetic material into common baker's yeast. This process induces the yeast

to produce an antigen, which is then purified. The purified antigen, when combined with an *adjuvant*, a substance that stimulates the immune system, results in a safe and very effective vaccine.

Recombinant Vector Vaccines

A vaccine *vector*, or carrier, is a weakened virus or bacterium into which harmless *genetic material* from another disease-causing organism can be inserted.

The vaccinia virus, the virus that causes cowpox, is now used to make *recombinant vector vaccines.* In the submicroscopic world of viruses, vaccinia is relatively large and has ample room to accept additional genetic fragments. A vaccinia virus with several genes from the human immunodeficiency virus (HIV) is currently being tested as a vaccine for acquired immune deficiency syndrome (AIDS). In addition, a close relative of vaccinia, canarypox virus, engineered with harmless fragments of HIV, is being tested in human volunteers as a vaccine for AIDS.

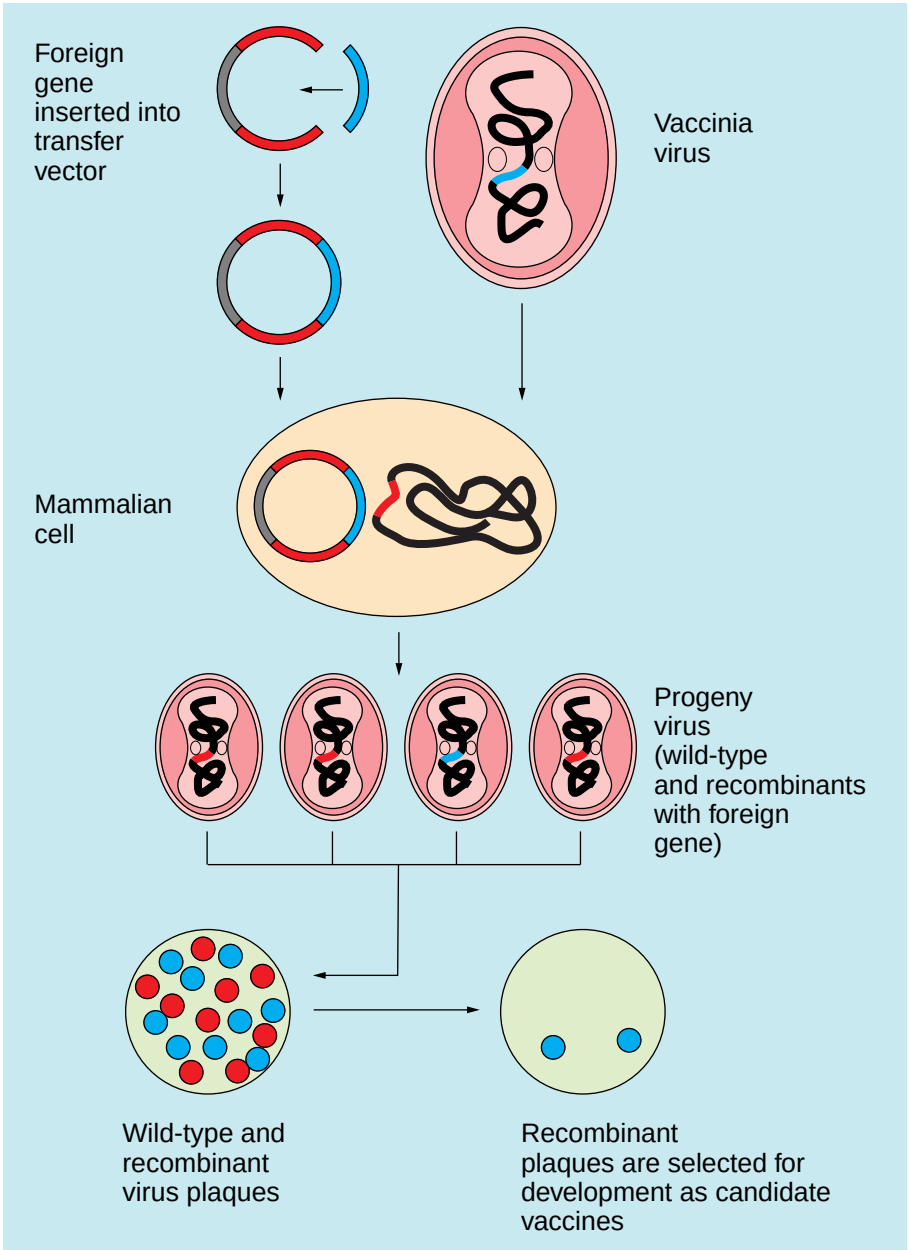
Similarly, scientists are testing a weakened bacterium—salmonella—to carry portions of such microbes as the hepatitis B virus. Currently no recombinant vector vaccines are licensed for general use in the United States.

Vaccine Development and Testing

To be approved for general use, a candidate vaccine must go through a long period of testing and validation. The time between discovery of a disease agent and production of a widely available vaccine has been as long as 50 years. Today, with biological synthesis and recombinant vaccine development techniques, the length of time from basic research to availability of a licensed product can sometimes be greatly reduced.

Basic Research and Development

Basic research focuses on biochemistry and physiology and on mechanisms that disease-causing microbes use to cause damage. Such research also takes into account the biophysical characteristics of



Vaccinia virus is recombined in a mammalian cell with a foreign gene. The vaccinia viruses produced are both wild-type viruses and new, recombinant viruses. These recombinant viruses are isolated and used to develop a safe, effective vaccine.

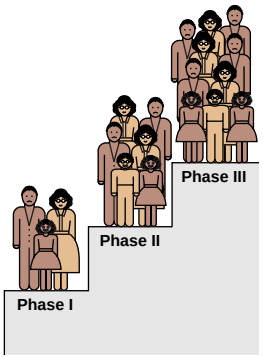
the organisms that might be used in vaccines or drugs to prevent or interrupt the disease process.

To develop a candidate vaccine, scientists test vaccine preparations in cell-culture, and often eventually in animals such as mice, guinea pigs, or even monkeys. In some cases, computers can help researchers visualize the vaccine candidates in three dimensions to predict how vaccine antigens will interact with the immune system. If the vaccine candidate is shown to be promising throughout the *preclinical* evaluations, it can become an *investigational vaccine.*

An investigational vaccine is one that successfully has gone through basic research and developmental processes, often including preclinical trials in animals, and has been approved by the U.S. Food and Drug Administration (FDA) for use in human volunteers in clinical trials.

Clinical Studies

Clinical studies rely entirely upon the participation of volunteers, people who contribute their time and energy for the advancement of science and improved health care for all. Thousands of volunteers of all ages and from all walks of life have participated in these studies. A typical volunteer in a vaccine study agrees to be given the vaccine, makes frequent visits to a clinic for evaluation, participates in medical testing, and provides blood or tissue samples that will be used in assessing the vaccine's safety and potential effectiveness. Unlike the boy vaccinated by Dr. Jenner 200 years ago, volunteers today must sign an informed consent document indicating their understanding of the study, its risks, and their willingness to participate.



Before a vaccine is licensed, researchers carefully evaluate its safety and effectiveness in many volunteers.

A candidate vaccine undergoes three phases of clinical trials before it can be licensed for public use. Phase I trials, to determine the safety of various doses of the vaccine, usually begin with small numbers of volunteers, and then expand to include more volunteers if the vaccine appears to be safe.

Steps in Vaccine Development

Understanding the disease
- Recognition of disease
- Diagnosis
- Location and identification of disease agent in nature
- Studies of extent of human disease
- Studies on how the agent damages the body and how the body's defenses react
- Studies of naturally acquired immunity

Understanding the disease agent
- Biochemical and biophysical description and characterization
- Growth in cell culture
- Analysis of antigens and genetic properties
- Studies of infection in animals

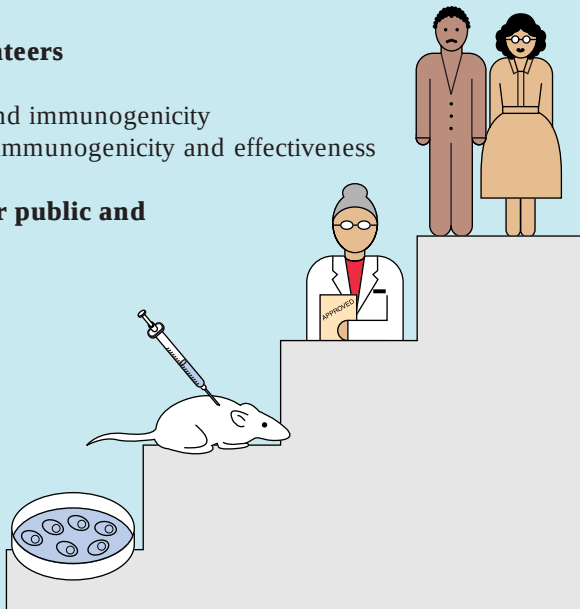
Developing a vaccine candidate
- Inactivating or weakening the disease agent
- Selection and purification of an appropriate antigen to stimulate the immune response
- Selection of adjuvants
- Demonstration of stability and lack of harmful properties in animals
- Stimulating a protective immune response in animals
- Production of pilot lots

Testing vaccines in volunteers
- Phase I studies: safety
- Phase II studies: safety and immunogenicity
- Phase III studies: safety, immunogenicity and effectiveness

Production of vaccine for public and commercial use

Licensing of the vaccine

Professional and public acceptance



Phase II trials, to determine whether the vaccine is safe and immunogenic, are open to hundreds of volunteers. The vaccine is tested for safety, for its ability to evoke an immune response, and for its potential to prevent disease.

Phase III trials are large-scale *efficacy* studies, often in thousands of individuals, to confirm that the vaccine safely prevents disease. A vaccine is considered successful if its overall effect is beneficial; it should prevent disease, and any side effects should be minimal. If the disease the vaccine is designed to prevent is rare in the United States, Phase III trials may be conducted in a country where the disease is prevalent. In the cases of such international cooperation, each government signs an agreement and expects its citizens to benefit from the study.

Side Effects and Adverse Reactions

The most common side effects of vaccines include low-grade fever, soreness and redness at the site of the injection, or sometimes body aches for up to 24 hours after vaccination. These minor side effects of a vaccine are far preferable to having the disease.

The extensive testing that a vaccine undergoes before it is licensed for public use is conducted, in part, to assure safety as much as possible by closely observing large numbers of volunteers for harmful side effects. But no matter how thorough the testing, it is impossible to allow completely for the extensive variation among individuals, their immune systems, and their reactions to the introduction of new substances into their bodies. Serious systemic reactions to vaccines can occur, although they are very rare. The FDA and the Centers for Disease Control and Prevention monitor vaccine distribution and use. Information about adverse reactions to a vaccine is collected even after the vaccine is licensed for general use. Both organizations record any incident of a serious reaction and follow up on any re-evaluation of the vaccine that is necessary.

NIAID's Role in Basic and Clinical Research

Basic research conducted and supported by the National Institute of Allergy and Infectious Diseases is helping scientists understand more about infectious microbes and human immune responses. From this understanding has come the development of vaccines and other tools needed to prevent many infectious diseases and immune system disorders. The goal of these efforts is not only to protect individuals from serious infections; but eventually to eradicate diseases, as we have seen with smallpox.

In clinical research, NIAID revolutionized the classical but cumbersome, piecemeal approach to clinical vaccine studies by designing a network of vaccine and treatment evaluation units, and more recently, an international network for testing vaccines to prevent infection with HIV. Testing sites are based at leading university medical research centers, public health departments, and community clinics. Investigators working within these networks and other NIAID-supported researchers played major roles in the clinical studies required for licensing of vaccines for Hib meningitis and of new *acellular* pertussis vaccines.

The Children's Vaccine Initiative

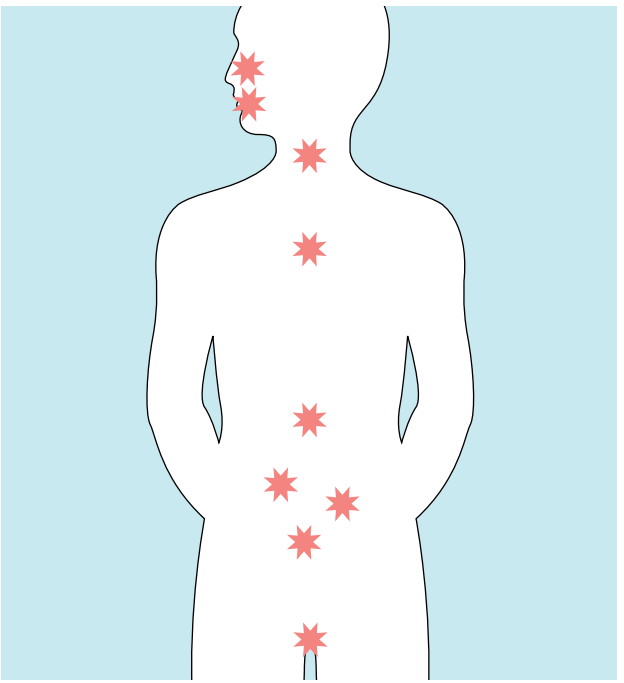
NIAID has been recognized by Congress as the lead agency to provide the scientific and programmatic direction for the Children's Vaccine Initiative (CVI). The CVI, a worldwide public health effort, combines the efforts of many international scientists and representatives of the United Nations International Children's Emergency Fund, the World Health Organization, the World Bank, The United Nations Development Program, the Rockefeller Foundation and vaccine manufacturers, biotechnology firms, and national research agencies. The CVI has made impressive strides towards its goal of universal immunization. Already 80 percent of all children in the United States receive their initial immunizations by their first birthdays. NIAID is making progress toward achievable goals, such as making existing vaccines safer and more effective and improving vaccines so that fewer doses will be needed.

Vaccines of the Future

Currently scientists are pursuing many promising new strategies in vaccine development and exploring novel ways to administer vaccines. The following descriptions of just a few of these innovative ideas provide a preview of safer, more effective ways to fight disease.

Exposing *mucosal membranes* to vaccines is a strategy that can produce an immune response in a less-stressful and better targeted manner. Mucosal membranes are located throughout our bodies, but are most accessible in the lungs, nose, mouth, throat, gastrointestinal tract, rectum and vagina. The oral polio vaccine, in use since the 1950s, is an early example of the effectiveness of this strategy. Another possible mucosal route of administration is through the nose, and flu vaccines may soon be widely available in a nasal spray. Researchers have shown that the route of entry a disease-causing organism takes is often an effective vaccine route as well.

Many vaccine improvements may result from progress in designing better adjuvants. At present, only an

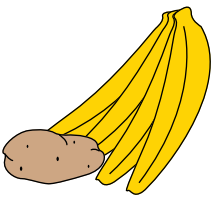


Mucosal membranes, located throughout the body and concentrated at entryways, can produce a protective immune response when stimulated by a vaccine.

aluminum salt called alum is approved as an adjuvant by the FDA, but scientists are studying many new natural and synthetic compounds.

Scientists are also looking at new ways of presenting the vaccine to the immune system. *Microspheres*, tiny spheres containing bits of antigenic material, show promise in that they can release small doses of vaccine over extended periods of time as the microspheres gradually dissolve in the body. This means that someone may be able to receive two or three doses in just one administration of vaccine.

Perhaps the most exciting new vaccine technique is introducing pure genetic material directly into the body. This genetic material, called "naked DNA," encodes a few proteins from a disease-causing organism. The DNA is then incorporated into the body's own cells, which make the proteins encoded by the new DNA. It is these proteins that are recognized as foreign and stimulate the immune system. In this way, the DNA will have an effect similar to that of a live, attenuated vaccine. In effect, the DNA will produce antigens for years and induce strong, long-lasting immunity. At the same time, the exclusion of genes that are critical to the disease-causing organism's survival will assure that the vaccines are safe and do not actually cause disease.



Researchers are also exploring ways to create edible vaccines. By genetically engineering plants to incorporate synthetic antigens, scientists may be able to develop a banana or potato, for example, that will produce protective immunity when eaten. Obviously, such a vaccine technique would greatly simplify immunization for many people of the world.

Vaccines remain among the most powerful tools we have for disease prevention, and advances in biotechnology have ushered in a new era in vaccine development that holds even more promise for improving public health. NIAID remains a leader in the discovery and testing of new and improved vaccines and will continue to nourish this exciting renaissance in vaccine development.

Glossary

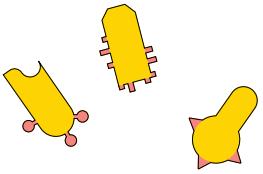
acellular vaccine—devoid of whole cells. Acellular vaccines contain only portions of cellular material.

active immunity—immunity produced by the body in response to stimulation by a disease-causing organism (naturally acquired active immunity) or by a vaccine (artificially acquired active immunity).

adjuvant—a substance sometimes included in a vaccine formulation to enhance the immune-stimulating properties of a vaccine.

antibody—soluble protein molecule produced and secreted by B cells in response to an antigen and capable of binding to that specific antigen.

antibody-mediated immunity (humoral immunity)—immune protection provided by B cells which secrete antibodies in response to antigen (as distinct from that provided by the direct action of immune cells, or cellular immunity).



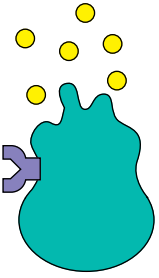
antigen—a substance that provokes an immune response.

B cells—small white blood cells crucial to the immune defenses. Also known as B lymphocytes, they are derived from bone marrow and develop into plasma cells, which produce antibodies.

bone marrow—soft tissue located in the cavities of the bones. The bone marrow is the source of all blood cells.

cell-mediated immunity (cellular immunity)—immune protection provided by the direct action of immune cells (as distinct from that provided by soluble molecules such as antibodies).

complement—a complex series of blood proteins whose action "complements" the work of antibodies. Complement destroys antibody-coated cells, produces inflammation, and regulates immune reactions.



conjugate vaccine—a vaccine in which proteins that are easily recognizable to the immune system are linked to the outer coat of the disease-causing organism to promote an immune response.

cytotoxic T cells—a subset of T lymphocytes that can kill other cells infected by viruses, fungi or certain bacteria, or cells transformed by cancer.

efficacy—in vaccine research, the ability of a vaccine to produce a desired clinical effect, such as protection against a specific disease, at the optimal dosage and schedule in a given population. A vaccine may be tested for efficacy in Phase III studies if it appears to be safe and shows promise in smaller Phase I and II studies.

epitope—a unique shape or marker carried on an antigen's surface, which triggers a corresponding antibody response.

formalin—a solution of water and formaldehyde, used as an antiseptic, disinfectant or fixative.

genetic material—deoxyribonucleic acid (DNA) that carries the directions a cell uses to perform a specific function, such as making a given protein.

Haemophilus influenzae type b (Hib)—a bacterium found in the respiratory tract that causes acute respiratory infections, including pneumonia, and other diseases such as meningitis.

helper T cells—a subset of T cells that typically carry the CD4 marker and are essential for turning antibody production on, activating cytotoxic T cells, and initiating many other immune responses.

humoral immunity—immune protection provided by soluble factors such as antibodies, which circulate in the body's fluids, primarily serum and lymph. (See *antibody-mediated immunity*.)

immunogenic—capable of stimulating an immune response (immunogenicity).

immunosuppressive—capable of reducing immune responses. For instance, drugs given to prevent transplant rejection are immunosuppressive.

inactivated toxins—organic toxins, such as those produced by bacteria and viruses, that have been killed by chemical means, heat, or irradiation, and are no longer capable of causing disease.

inactivated vaccine—(killed vaccine) a vaccine made from a whole virus or bacterium whose biological ability to grow or reproduce is ended.

investigational vaccine—a vaccine that has been approved by the Food and Drug Administration for testing in humans, but that has not yet completed evaluation and been accepted for licensure and public use.

killer T cells (cytotoxic T cells, cytotoxic lymphocytes, CTLs)—a subset of T cells that can kill cancer cells and cells infected with viruses, fungi or certain bacteria.

live, attenuated vaccine—a vaccine whose biological activity has not been inactivated, but whose ability to cause disease has been weakened.

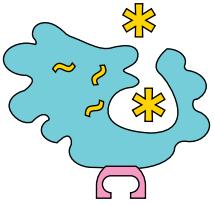
lymph—a transparent, slightly yellow fluid that carries lymphocytes, bathes the body tissues, and drains into the lymphatic vessels.

lymph nodes—small bean-shaped organs of the immune system, distributed widely throughout the body and linked by lymphatic vessels. Lymph nodes are gathering sites of B, T, and other immune cells.

lymphatic vessels—a bodywide network of channels, similar to the blood vessels, that transport lymph to the immune organs and into the bloodstream.

lymphocytes—small white blood cells produced in the bone marrow and thymus that are essential in immune defense.

lymphoid organs—organs of the immune system, where lymphocytes develop and congregate. They include the bone marrow, thymus, lymph nodes, spleen, and various other clusters of lymphoid tissue, such as the appendix. The blood vessels and lymphatic vessels also can be considered lymphoid organs.



major histocompatibility complex (MHC)—a large set of cell surface molecules in each individual, encoded by genes. MHCs serve as unique biochemical markers of individual identity.

macrophage—a large and versatile immune cell that acts as a microbe-devouring phagocyte, an antigen-presenting cell, or an important source of immune secretions.

memory cell—a subset of T cells and B cells that have been exposed to specific antigens and can then respond more readily when the immune system encounters the same antigens again.

microbe—a minute living organism, such as a bacterium or virus.

microspheres—tiny, microscopic spheres that can carry vaccines or drugs and can pass easily through the body's tissues.

mucosal membranes—the moist tissues lining body cavities or passages that have an opening to the external world, such as the mouth, nose, rectum or vagina. Mucosal immunity depends on immune cells and antibodies being present in the linings of the reproductive, respiratory, gastrointestinal tracts, and other mucosal membranes.

mutate—to change a gene or unit of hereditary material that results in a new inheritable characteristic.

naked DNA vaccine—vaccine made up of deoxyribonucleic acid that is not encased or encapsulated. In naked DNA vaccines, genetic material is injected directly into the vaccine recipient.

naturally acquired immunity—immunity produced by immune cells passed from mother to fetus or by the body in response to exposure to a disease-causing organism.

passive immunity—immunity resulting from the transfer of cells or antibodies or antiserum produced by another individual.

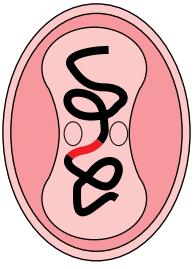
Peyer's patches—a collection of lymphoid tissues in the intestinal tract.

phagocyte—an immune cell that is able to ingest and destroy microbes and other foreign matter.

potency—the strength of a substance. In vaccines, one of the qualities that makes a vaccine protective.

preclinical—a phase of study of a vaccine or drug that is completed before clinical studies are carried out in people. Preclinical studies may be conducted in cells or in animals.

protective immunity—complete resistance to disease, whether long-lasting or temporary.

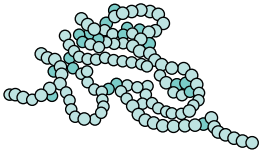


recombinant DNA technology—the technique by which genetic material from one organism is inserted into a foreign cell or another organism in order to mass-produce the protein encoded by the inserted genes. (Also called recombinant genetic engineering.)

recombinant genetic engineering—See *recombinant DNA technology*.

recombinant subunit vaccine—a subunit vaccine made using recombinant DNA technology. (See *subunit vaccine*.)

recombinant vector vaccine—a vaccine that combines a vector—a harmless bacterium or virus used to transport an antigen into the body to stimulate protective immunity—and an antigen or immunogen from an organism other than the vector.



spleen—a lymphoid organ in the abdominal cavity that is an important center for immune system activities.

Streptococcus pneumoniae—a bacterium found in the respiratory tract that is a common cause of pneumonia.

subunit vaccine—a vaccine that uses one or more components of a disease-causing organism, rather than the whole, to stimulate an immune response.

T cells—small white blood cells that orchestrate or directly participate in immune defenses. Also known as T lymphocytes, they mature in the thymus.

thymus—a primary lymphoid organ, high in the chest, where T lymphocytes proliferate and mature.

toxoid—an inactivated or killed organic toxin used to immunize against specific bacteria.

vector—in vaccine technology, a bacterium or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport genes coding for antigens into the body to induce an immune response.

virulent—toxic, causing disease.